IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: María Teresa Moreno Flores et al.	Art Unit	: 1632
Serial No.	: 10/564,466	Examiner	: Thaian N. Ton
Filed	: October 27, 2006	Conf. No.	: 5995
Title	: REVERSIBLY IMMORTALISED OLFACTORY ENSHEATHING GLIA AND THEIR USE TO PROMOTE NEURONAL REGENERATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

This paper is responsive to a Restriction Requirement having a notification date of December 16, 2008 ("the RR"). Applicants elect Group II, "claim(s) 7, 11, 13-19, and 22, drawn to a population of human functional OEG cells (RR, page 2). This election is made **with** traverse, which will be addressed in the discussion below.

[I] The present application is the U.S. National Stage of International Application No. PCT/GB2004/003149, filed on July 19, 2004. As such, the present application is subject to unity of invention practice in accordance with 37 CFR 1.475 and 1.499 (see MPEP § 1896).

[II] 37 CFR 1.475 provides as follows (emphasis added):

> a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). **Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features.** The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
>
> (b) **An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories**:
>
> (1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

(c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.

(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c).

(e) The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

[III] Presently, the Office is requiring that Applicants elect one of the following groupings of claimed subject matter (Office Action, page 2):

I. Claims 1-6 and 9-10, drawn to methods of making populations of human functional olfactory ensheathing glia (OEG) cells;

II. Claims 7, 11, 13-19 and 22, drawn to a population of human functional OEG cells;

III. Claims 8, 12, 20, 25, and 28, drawn to methods of treating a patient for neural damage and a pharmaceutical composition; and

IV. Claims 21 and 27, drawn to cell libraries comprising a collection of reverse-immortalized OEG human cells.

The RR further states, in part (RR, page 3, emphasis added):

Unity of Invention is lacking in the instant claims because they fail to contribute over the prior art **because the technical feature linking the groups is known in the prior art. The technical feature linking the groups appears to be OEG cells. However, Ramón-Cueto (Applicants' IDS) teaches olfactory ensheathing glia (OEG), the specific characteristics of the cells, as well as**

methods to isolate them. Therefore, the technical feature linking the inventions Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

[IV] This is respectfully traversed, and it is respectfully pointed out that no unity of invention rejection was raised by the International Search Authority in connection with PCT/GB2004/003149, the PCT application upon which the present U.S. national phase application is based.

This paper is being filed concurrently with a Preliminary Amendment ("the PA"), and Applicants respectfully request the restriction requirement be reconsidered and withdrawn in view of the amendments set forth in the PA. These amendments, however, should not be construed as acquiescence on the part of Applicants to the Office's grounds for restriction. Rather, the amendments set forth in the PA are intended to further clarify the special technical feature that is shared by the present claims, i.e., human olfactory ensheathing glia (OEG) cells obtained by reversible genetic modification (i.e., reverse-immortalised and reversibly-immortalised) (see e.g. see page 6, lines 2-4; page 6, lines 9-21; page 7, line 30 – page 8, line 9 of the specification), that have the ability to promote axonal regeneration from adult CNS neurons. This is discussed in more detail below.

[A] *Summary of Claimed Subject Matter as Presently Amended*

Claim 1 as presently amended is directed to a method of making a population of **reverse-immortalised** human olfactory ensheathing glia (OEG) cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into a patient, which includes:

a) providing a sample of primary human OEG cells;
b) immortalizing the OEG cells by transforming the OEG cells with a vector comprising a removable DNA segment containing an oncogene or combination of oncogenes, thereby producing immortalised OEG cells;
c) growing the immortalised OEG cells;
d) selecting those immortalised OEG clonal cell lines which maintain the property of promoting axonal regeneration from adult CNS neurons; and

e) removing the DNA segment from the immortalised OEG cells, the removal resulting in the production of the population of reverse-immortalised human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplantation into the patient.

Claim 7 as presently amended is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration, for transplantation into a patient, producible by the method of claim 5 (which depends from claim 1 *supra*).

Claim 8 as presently amended is directed to a method of treating a patient for neural damage, comprising transplanting into the patient a sufficient quantity of the **reverse-immortalised** human OEG cells of claim 7 to provide promotion of neuronal regeneration in the neuronal injured region of the patient.

Claim 9 as presently amended is directed to a method of making a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons, for transplanting into a patient, which includes:

a) providing a sample of primary human OEG cells;

b) immortalizing the OEG cells by transforming the OEG cells with a vector comprising a removable DNA construct containing an oncogene or a combination of oncogenes, a selectable marker gene, and a gene encoding herpes simplex virus thymidine kinase, the genes together being flanked on either side by loxP sites;

c) growing the immortalised human OEG cells;

d) selecting those immortalised OEG clonal cell lines which maintain the property of promoting axonal regeneration from adult CNS neurons; and

e) reversing the immortalization of the human OEG cells by removing the DNA construct from the immortalised OEG cells, the removing being accomplished by introducing into the immortalised OEG cells a gene encoding Cre recombinase to effect excision of the DNA construct at the loxP sites, the excision resulting in the production of the population of reverse-immortalised human OEG cells, which have the ability to promote axonal regeneration from adult CNS neurons for transplanting into a patient.

Claim 11 as presently amended is directed to a population of **reverse-immortalised** human OEG cells, which have the ability to promote axonal regeneration, for transplantation into a patient, producible by the method of claim 9.

Claim 12 as presently amended is directed to a method of treating a patient for neural damage, comprising transplanting into the patient a sufficient quantity of the **reverse-immortalised** human OEG cells of claim 11 to provide promotion of neuronal regeneration in the neuronal injured region of the patient.

Claim 27 as presently amended is directed to a cell library comprising a collection of **reverse-immortalised** human OEG cells prepared according to the method of claim 9.

Claim 13 as presently amended is directed to a **reversibly-immortalised** human OEG cell, which has the ability to promote axonal regeneration from adult CNS neurons, comprising a primary human OEG cell transformed with a vector comprising a DNA construct comprising two recombinase target sites that flank an oncogene or combination of oncogenes which confers immortalization to the OEG cell, wherein the immortalization is reversible by excision of the DNA construct by cleavage at the recombinase target sites when the target sites are exposed to a recombinase that specifically recognizes the target sites.

Claim 18 as presently amended is directed to a cell line comprising a population of the **reversibly-immortalised** human OEG cell of claim 13.

Claim 19 as presently amended is directed to a **reverse-immortalised** human OEG cell, which has the ability to promote axonal regeneration from adult CNS neurons upon transplantation into a patient, produced by exposing the DNA construct within the reversibly-immortalised human OEG cell of claim 13 to a recombinase that excises the DNA construct by cleavage at the recombinase target sites.

Claim 20 as presently amended is directed to a method of treating a patient for neural damage, comprising transplanting into the patient a sufficient quantity of the **reverse-immortalised** human OEG cells of claim 19 to provide promotion of neuronal regeneration in the neuronal injured region of the patient.

Claim 21 as presently amended is directed to a cell library comprising a population of **reverse-immortalised** OEG human cells, which have the ability to promote axonal regeneration from adult CNS neurons, prepared according to the method of claim 1.

Claim 22 as presently amended is directed to a **reverse-immortalised** functional human olfactory ensheathing glia (OEG) cell line, which has the ability to promote axonal regeneration from adult CNS neurons.

Claim 25 as presently amended is directed to a pharmaceutical composition comprising a **reverse-immortalised** human OEG cell line as defined in claim 22, and a pharmaceutically acceptable carrier.

Claim 28 as presently amended is directed to a method of treating a patient for neural damage, comprising transplanting into the patient a sufficient quantity of the **reverse-immortalised** human OEG cells of the cell line of claim 22 to provide promotion of neuronal regeneration in the neuronal injured region of the patient.

New claim 33 is directed to a method of making **reversibly-immortalised** human OEG cells.

[B] As can be seen, the presently amended claims share a special technical feature, which is reversibly genetically modified (**reverse-immortalised** and **reversibly-immortalised**) human OEG cells that have the ability to promote axonal regeneration from adult CNS neurons.

A reversibly-immortalised human OEG cell is one that has been subjected to a particular genetic modification, and is presently in an immortalised state, but can be returned to a non-immortalised state at a later time (see, e.g., page 11, lines 10-11). As explained in the specification, this cell has been subjected to a process whereby the OEG cells are immortalised by a means that enables them to be returned to a non-immortalised state at a later time. This is achieved by transforming the OEG cells with a vector comprising a removable DNA construct containing an oncogene or combination of oncogenes (details given on page 7, line 29 – page 8, line 9).

A reverse-immortalised human OEG cell is **also** one that has been subjected to the same genetic modification described in the prior paragraph, but now exists in a non-immortalised state

(see page 11, lines 14-15). Such a state can be achieved by excision of the previously incorporated DNA construct (= "*DNA segment*" above; "*segment*" and "*construct*" are indistinctly used throughout the specification for the same term), containing an oncogene or combination of oncogenes (*supra*).

It is noted that the OEG cells obtained according to the present invention closely resemble primary OEGs in their molecular markers (see page 5, lines 29-30 of the specification). Further, they maintain their ability to promote axonal regeneration from adult neurons, even when the immortalization process is reversed (page 5, lines 30-32), i.e., these observations apply both to reversibly-immortalized and reverse immortalized OEG cells. Any of the OEG cells subjected to the reversible genetic modification (i.e. reversibly-immortalised and reverse-immortalised OEG cells) are thus not identical to primary OEG cells, i.e. they are different from primary OEG cells. .

In short, the reversibly-immortalised and reverse-immortalised human OEG cells of the claims present molecular characteristics that distinguish them from the naturally occurring human OEG described in Ramón-Cueto. It is evident therefore that the reversibly-immortalised and reverse-immortalised human OEG cells of the claims are **not** the same as the naturally occurring human OEG described in Ramón-Cueto. Indeed, Ramón-Cueto does not disclose or suggest the reversibly-immortalised and reverse-immortalised human OEG cells of the claims, and the requirement for restriction should be withdrawn for at least this reason.

[C] Finally, 37 CFR § 1.475(b)(3) states that a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn to a combination of "[a] product, a process specially adapted for the manufacture of the said product, and a use of the said product" (*supra*). Here are claimed reversibly-immortalised and reverse-immortalised human OEG cells (as well as cell lines, cell libraries, and pharmaceutical compositions containing the same). As discussed above, reversibly-immortalised and reverse-immortalised human OEG cells are technically linked to one another in at least two ways: (i) both are subjected to the same reversible genetic modification, consisting in their transformation with a vector comprising a removable DNA construct/segment"; and (ii) have the ability to promote axonal regeneration from adult CNS

neurons. Also claimed are processes specially adapted for the manufacture of reverse-immortalised and reversibly-immortalised human OEG cells (claims 1, 9 and 33 and claims dependent therefrom), as well as uses of reverse-immortalised human OEG cells (claims 8, 12, 20, and 28-32). Applicants submit that the present claims satisfy 37 CFR 1.475(b)(3) and therefore have unity of invention for at least the reasons provided above. In view of the foregoing, Applicants respectfully request that claims 1-22, 25, 27, and 28 and new claims 29 to 33 be examined in concert.

The fee in the amount of $2,350 for Five Month Extension of Time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14829-003US1 / F/USP288389.

Respectfully submitted,

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